Resection margins in rectal cancer

Miha Lučovnik, Mirko Omejc

University Medical Centre Ljubljana, Department of Abdominal Surgery, Ljubljana, Slovenia

Summary

Objective: Knowledge of resection margin status as a prognostic factor in rectal carcinoma has increased profoundly in recent years. The limit for oncologically safe distal clearance continues to decrease and is still being debated. On the other hand radial clearance has been shown to be a very important oncologic concept since positive circumferential margin after total mesorectal excision is associated with high risk of local recurrence and distant metastases. We tried to address the relative influence of different distal and circumferential resection margin lengths on survival. Patients and methods: 117 rectal cancer patients who underwent a potentially curative R0 resection including total mesorectal excision without preoperative chemoradiotherapy between 1/1994 and 12/1999 were included in the study. Resection margins lengths were measured on a pinned specimen after fixation. Results: There was no significant difference in 5-year survival when distal resection margin was ≤ 1 cm comparing to > 1 cm (p = 0.91), but 5-year survival was adversely affected by circumferential margin of ≤ 2 mm comparing to > 2 mm (p = 0.0095). In multivariate analysis, independent prognostic factors were Dukes stage and length of the circumferential margin but not the length of the distal margin. When only the patients undergoing sphincter saving procedure were analysed, Dukes stage was still an independent prognostic factor while circumferential and distal resection margin lengths were not. Conclusion: Circumferential resection margin has been shown to be more important in determining survival than distal resection margin. A distal margin of 1 cm or less may be acceptable in most patients; therefore a sphincter saving procedure can also be considered in very low lying tumours. In these tumours, however, the risk of CRM involvement during low anterior resection seems to be increased compared to abdominoperineal excision. This may be due to the natural narrowing of the mesorectum caudally or to the "coning in" on the rectum by the surgeon to avoid defunction.

Key words: *rectal cancer, resection margin, survival*

INTRODUCTION

Adenocarcinoma of the colon and rectum has become one of the major health problems in the western countries due to its rapidly increasing incidence in recent decades. It is currently the second most common cause of death by cancer in the western world [1]. According to the Slovene Cancer Registry, colorectal cancer has already become the most common among all cancers in Slovenia [2]. Approximately one third of all colorectal cancers arise in the rectum (0–15 cm from the anal verge) [1,3].

Fortunately not only the incidence of rectal carcinoma has been increasing during the last decades. Technical innovations together with a better understanding of pelvic anatomy and the behaviour of rectal tumours have resulted in some radical changes in the surgical and nonsurgical treatment of these neoplasms. These changes have considerably improved outcome and survival [4]. Outcome in rectal cancer depends on stage, use of neoadjuvant and adjuvant chemoradiation and technical aspects of surgical excision [1,3]. One of the main objectives of surgical treatment is to provide adequate safety margins of healthy tissue around the tumour, since positive resection margins are associated with high risk for local recurrence, distal metastases and eventually death [3,5,6]. The aim of our study was to address the relative contributions of distal resection margin (DRM) and circumferential resection margin (CRM) status towards survival.

Distal resection margin

Introduction of the stapling technique, increased understanding of the rectal cancer oncology and the role of neoadjuvant radiotherapy and chemoradiotherapy have resulted in an increasing number of patients undergoing sphincter saving resections [7]. This caused much debate concerning the extent of distal clearance of the tumour. The presence of microscopic distal intramural spread found in some patients led to the rule of tumour clearance extending at least 5 cm into uninvolved tissue [8]. This so called "5 cm rule" was changed to the "2 cm rule" in the 1980s. 2 cm clearance was considered adequate since distal intramural spread greater than 1 to 2 cm was found to be related to advanced and metastatic tumours in which the length of the DRM has little importance in determining outcome [9]. Today many authors believe that DRM of 1 cm for T1-2 lesions and 2 cm for T3-4 tumours is oncologically safe [3,5]. However, several studies showed that preoperative chemoratiotherapy may

justify DRM of 1 cm or even less as a result of tumour regression [10–12]. Studies in rectal cancer patients receiving postoperative chemoradiotherapy and in N0 rectal cancer patients receiving no adjuvant therapy also showed that DRM of 1 cm or even less may be sufficient [12,13]. Many therefore now accept any distal margin as long as the margin is microscopically clear [14]. The optimal length of DRM is not yet determined at the moment. The purpose of this study was to show whether DRM of less than 1 cm negatively influences the survival of rectal cancer patients not treated with pre or postoperative chemoradiation.

Circumferential resection margin

In recent decades, the circumferential resection margin has been shown to be a more important oncologic concept than the DRM in rectal cancer surgery [6,15–17]. Tumours of the rectum disseminate proximally and radially but rarely distally since the principal lymphatic drainage of the rectum is to nodes in the mesorectum and then nodes along superior rectal and inferior mesenteric arteries [5]. The term mesorectum designates the fatty and connective tissue with vessels, lymphatics and lymph nodes surrounding the rectum and is enveloped by fascia. The concept of adequate excision of the mesorectum, introduced by Heald and co-workers in the early 1980s, was an important step forward in the surgical treatment of rectal carcinoma [4]. The basic principles of mesorectum excision consist of sharp dissection under direct vision in the avascular planes between the mesorectum and the surrounding parietes. The objective of this "specimen oriented surgery" is an intact mesorectum with no tearing of the surface and no CRM involvement. In total mesorectum excision (TME) the mesorectum is completely excised downwards to the pelvic floor, in contrast to this, in partial mesorectum excision (PME) the mesorectum is transected at right angle to the rectal wall at a distance of 5 cm beyond the gross distal margin of the tumour. TME is indicated for carcinoma of the lower and the middle third while PME is considered sufficient for carcinomas of the upper third of the rectum [18].

The more traditional approach has been blunt dissection within the presacral space. This technique, however has great potential for leaving a substantial amount of mesorectal tissue behind and is associated with high rate of local recurrence (15–45 % versus < 10 % in TME) [18,19]. The main reason for this difference is probably the higher proportion of patients with clear CRM after TME since microscopic involvement of CRM correlates strongly with pelvic recurrence and eventually death independently of stage of disease [6,15–17].

A positive CRM is also associated with high risk of distant metastases [6]. When the carcinoma does not directly encroach on the CRM, the distance between the radial extent of the tumour and the resection margin at which CRM should be considered positive is not yet determined. Early studies suggested that the limit should be set at 1 mm, while a more recent Dutch trial showed that 2 mm margin also indicated high risk [6,18]. These differences support the idea that there is an exponential increase in rates of local recurrence, metastasis and death with decreasing CRM [17]. We examined the importance of different CRM and their influence on 5-year survival.

PATIENTS AND METHODS

Records of 162 consecutive patients receiving surgical treatment for adenocarcinoma of the rectum at our institution between 1/1994 and 12/1999 were reviewed. Cases with distant metastases at operation (n = 4), multiple tumours at operation (n = 5), emergency operation (n = 1), local tumour excision (n = 1) and locally non-complete resections (n = 26) were discarded. We also excluded 8 patients who received preoperative chemoradiotherapy, leaving 117 cases for the analysis.

Specimens were received unfixed, straightened without stretching and pinned on a board. CRM and DRM were measured on a histological slide after fixation.

Data on patient survival was found in the Slovene Cancer Registry.

The Kaplan Meier estimates of overall survival time in various prognostic factor categories (CRM, DRM and stage) were calculated and compared by means of log rank test. Multivariable analysis of survival was performed using Cox regression analysis. The limit of significance was set at $p \leq 0.05$.

RESULTS

A total of 117 patients (68 males, 49 females) with a median age of 64 years (range 29–86 years) were analysed in this study. All patients underwent a potentially curative R0 resection including TME without preoperative chemoradiotherapy. Sphincter saving resection was performed in 105 (89.7 %) cases. The remaining 12 (10.3 %) patients underwent APE. The location of the tumour was defined intraoperatively. 48 carcinomas lay in the upper, 43 in the middle and 26 in the lower third of the rectum. All procedures were performed by 11 different surgeons.

Comparison of estimated survival was made between patients with DRM > 1 cm and DRM ≤ 1 cm, between patients with CRM > 2 mm and ≤ 2 mm and between different Dukes stages. There was no significant difference in 5-year survival when DRM was ≤ 1 cm comparing to > 1 cm ($p = 0.8892$, fig. 1), but 5-year survival was adversely affected by CRM of ≤ 2 mm comparing to > 2 mm ($p = 0.0007$, fig. 2).

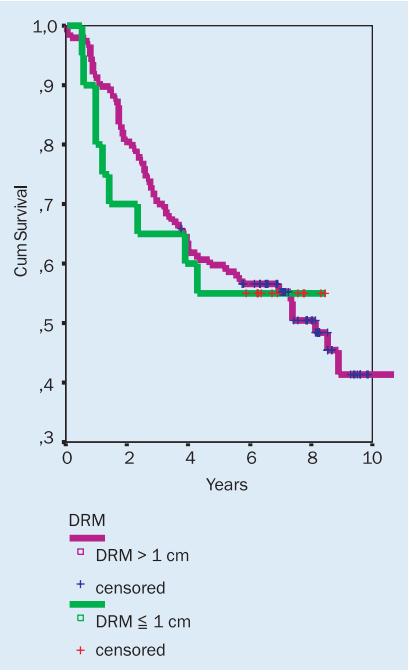

Fig. 1.
Comparison of cancer-specific survival for DRM > 1 cm and DRM ≤ 1 mm groups (log rank, p = 0.8892).

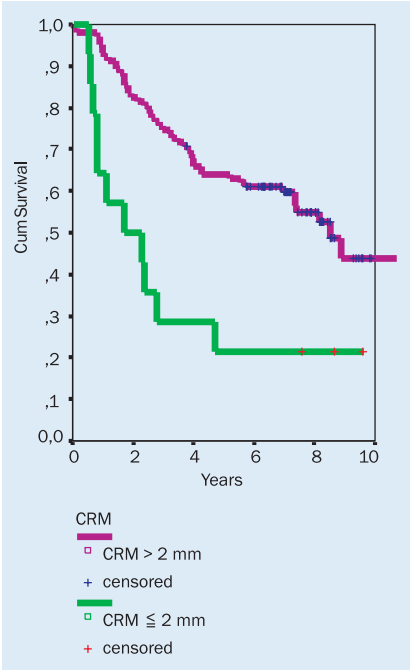

Fig. 2.
Comparison for cancer-specific survival for CRM > 2 mm and CRM ≤ 2 mm groups (log rank, p = 0.0007).

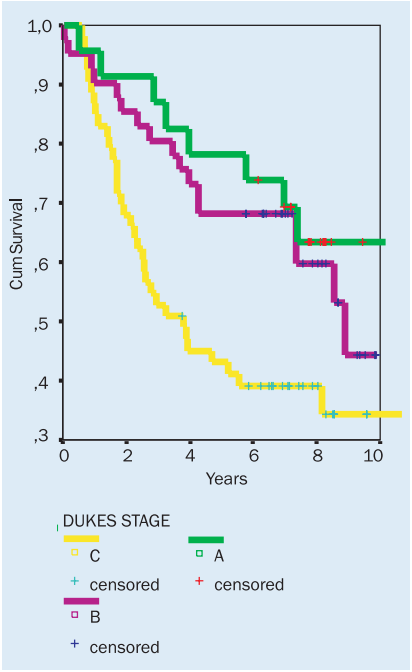

Fig. 3.
Comparison for cancer-specific survival for different Dukes stage groups (log rank, p = 0.0093).

Survival was also affected by stage of the disease as expected (p = 0.0093, fig. 3).

Multivariate analysis in a Cox regression model showed that the distance of the CRM and Dukes stage had an independent prognostic value for survival (p = 0.021 and p = 0.029 respectively) but the distance of the distal margin did not (p = 0.842).

Interestingly, when only the 105 patients after sphincter saving procedure were analysed, the picture was different. There was still a significant difference in survival between CRM > 2 mm and ≤ 2 mm groups (p = 0.0095, fig. 4) and no significant difference between DRM > 1 cm and DRM ≤ 1 cm groups (p = 0.9113, fig. 5). In the multivariate analysis, however, only the Dukes stage was an independent prognostic factor (p = 0.043) but the distance of the circumferential and distal margins were not (p = 0.119 and p = 0.896 respectively).

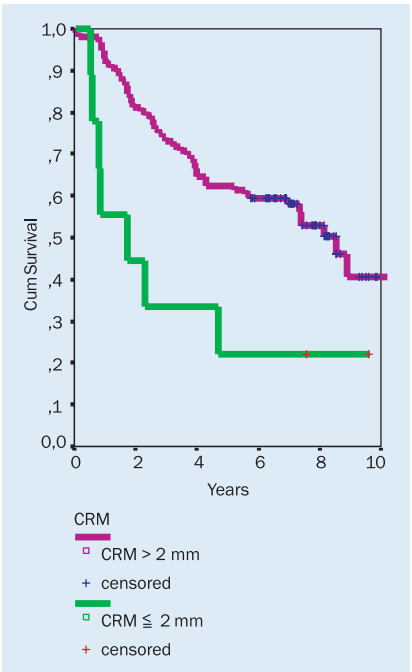

Fig. 4.
Comparison of cancer-specific survival for CRM > 2 mm and CRM ≤ 2 mm groups in patients undergoing sphincter saving procedure (log rank, p = 0.0095).

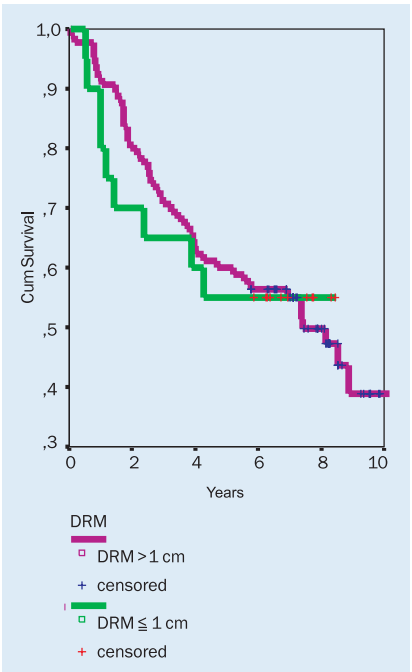

Fig. 5.
Comparison of cancer-specific survival for DRM > 1 cm and DRM ≤ 1 cm groups in patients undergoing sphincter saving procedure (log rank, p = 0.9113).

DISCUSSION

In assessing our data one should realise that it comes from a retrospective study. We have shown, however, that distal clearance of less than 1 cm may be appropriate for most rectal cancers. Strict adherence to the "2 cm rule" may therefore lead to unnecessary sacrifice of many sphincters.

Many authors have already shown that DRM < 1 cm does not seem to adversely affect survival [10–13]. Most of these studies included rectal cancer patients who received either preoperative or postoperative chemora-

diotherapy, which may theoretically eradicate any foci of distal intramural spread, and the DRM < 1 cm would be less likely to compromise the outcome in these patients [1,10]. In our study, however, only the population of patients treated with surgery alone, without chemoradiation was analysed. Our data therefore suggest that the length of distal clearance has little importance in determining survival as long as the margin is clear even in patients receiving no neoadjuvant or adjuvant therapy. The limit for sphincter saving resection appears to be functional rather than oncologic.

It should be stressed that when assessing the DRM, we focused on the distal intramural spread. Distal mesorectal spread, however, usually exceeds intramural spread, especially in advanced rectal cancer in which upward lymphatic flow is blocked [20–22]. Several authors have shown that incomplete removal of cancer deposits in the distal mesorectum contributes a great share to local recurrence [20–23]. The safe DRM of the mesorectum is still somehow controversial although many believe that 4 cm might be appropriate [21]. In lower rectal cancers this could be difficult to achieve since the mesorectum becomes narrowed and tampered deep within the pelvis [11,21,24]. A "close shave" of the rectal wall is therefore needed for a complete removal of the distal mesorectum [11].

We have also shown that CRM status and the extent of radial clearance is a more important predictor of disease survival than DRM. Pathologic studies from Quirke first drew attention to the CRM [15]. He and other authors showed that there is a strong relationship between finding of carcinoma at a distance of 1 mm or less from CRM and increased rates of local recurrence associated with poor survival [16,17]. In a large randomised trial a CRM of ≤ 2 mm was also associated with higher local recurrence rate and patients with CRM ≤ 1 mm had an increased risk of distant metastases [6]. Data on local recurrence rate was unavailable in our study, we showed however, that the presence of tumour cells within 2 mm from the CRM adversely affected survival and a margin of ≤ 2 mm between tumour and CRM should be considered positive. It should be noted again that we excluded patients who received neoadjuvant or adjuvant therapy. Its use can bias such studies because it theoretically has the potential to reduce both local and distant recurrence by treating micrometastatic disease [25].

When we looked at the relative influence of CRM on survival, the problem of adequate mesorectal clearance in low rectal cancer became evident again. The extent of radial clearance at CRM influenced survival independently of stage when all rectal cancer patients after potentially curative R0 resection were considered. This is in accordance with the literature [6,16,17]. When only patients after sphincter saving procedures were analysed, however, CRM was not an independent prognostic factor. This may be explained by the fact that the mesorectum tapers from the level of the origin of the levators and very little mesorectal tissue surrounds the lower rectal wall. In low anterior resection, the dissection plane is therefore closer to the tumour than in APR and the risk of CRM involvement increases. Clear lateral margins cannot be achieved, especially in locally advanced disease. This could explain why when only sphincter saving procedures are analysed, the prognostic value of CRM becomes dependent on the stage.

Apart from this "natural coning" of the mesorectum, the tendency of "coning in" on the mesorectum by the surgeon during low anterior resection may also explain our results. Although it should be avoided, "coning" of the mesorectum at the distal margin is implemented because the TME, in which the mesorectum is completely excised downwards to the pelvic floor, is associated with higher anastomotic leak rate probably due to the devascularisation of the rectal stump [4,26– 29]. It seems therefore reasonable to adopt a policy of temporary diverting loop ileostomy in cases with low anastomoses where most leaks occur.

The results of our study show that obtaining an adequate intramural DRM is of little value if the CRM is not clear. They also once more beg the question about discrepancy between theory and practice regarding TME.

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Correspondence to:
Mirko Omejc, MD, PhD
University Medical Center,
Department of Abdominal Surgery
Zaloška 7, 1525 Ljubljana
Slovenia
tel: 00386 41 740 383
email: mirko.omejc@mf.uni-lj.si